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Exploring Herbal Remedies For Skin Cancer: A Comprehensive Review

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Abstract

Skin cancer, ranked as the fifth most prevalent cancer, is a rising health threat, emphasizing the need for innovative treatments. Genetic mutations cause skin cell abnormalities leading to various cancers, especially melanoma. Current treatments, such as radiation therapy and chemotherapy, have limitations, necessitating advancements in technology and therapy. Early detection is crucial for effective intervention, and diagnostic methods encompass blood tests, imaging, biopsies, and genetic tests, followed by staging to determine disease severity. This review focuses on herbal remedies from medicinal plants like ursolic acid, genistic acid, luteolin, curcumin, and others, demonstrating anti-cancer properties in inhibiting proliferation and modulating molecular processes. Studies, primarily in vitro and animals, offer insights into their potential for skin cancer prevention. The review synthesizes diverse literature, providing nuanced insights into herbal remedies' molecular mechanisms for innovative therapeutic approaches. Emphasizing the importance of human trials, particularly for compounds like ursolic acid and genistic acid, is crucial for validating efficacy and safety. Herbal remedies align with WHO recommendations, holding promise for more effective and holistic skin cancer treatments. Ongoing research supports the integration of these compounds into treatment protocols, marking a hopeful frontier in combatting this pervasive disease.

Keywords: Skin cancer, Herbal remedies, Curcumin, Ursolic acid, Luteolin

1. INTRODUCTION

Skin cancer, the fifth most prevalent cancer, is projected to become a leading cause of death, potentially surpassing heart disease. With 18.1 million new cancer cases in 2018 and about 9.6 million related deaths, melanoma is estimated to represent 4% of new cases in women and 6% in men by 2023. Genetic flaws or mutations in skin cell DNA are the root cause of aberrant skin cell proliferation leading to skin cancer [1]. The epidermis, composed of melanocytes and epithelial cells, overlays the dermis housing sweat glands, blood

vessels, and hair follicles. Non-melanoma skin cancer (NMSC), comprising basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), typically starts in the epidermis. Around 25% of documented cases show a mole progressing to Multiple Myeloma (MM), often with a high recurrence rate, stressing the importance of early detection and eradication. Effective investment in technology and therapy is crucial due to skin cancer's significant impact on social and psychological well-being. Current treatments like radiation therapy, chemotherapy, and surgery, while commonly used, have drawbacks and can harm healthy cells. Photodynamic therapy (PDT) and photothermal therapy (PTT) offer potential tumor-ablative treatments, selectively targeting cancer cells [2].

Diagnosis involves a comprehensive evaluation and specific tests such as blood tests, imaging, biopsies, and genetic tests to pinpoint the ailment accurately. Staging, critical after diagnosis, determines the disease's extent and severity, influencing treatment decisions and prognosis prediction (refer **figure 1** and **figure 2**). It aids in tailoring treatment plans and providing patients with a clearer understanding of their condition and potential outcomes. Skin cancer is a pervasive disease affecting approximately one in every five individuals during their lifetime, but early identification has significantly lowered mortality rates [3]. Unrestrained growth of normal cells characterizes cancer, with two primary types: non-melanoma skin cancer (NMSC) and melanoma skin cancer [4]. NMSC, notably basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is prevalent in regions like North America, Australia, and New Zealand, with an estimated 1,042,056 new cases globally in 2018, linked to about 6% of all deaths. Ultraviolet (UV) radiation is a primary cause of NMSC, particularly affecting those with lighter skin tones. Genetic mutations in certain gene families, including CYP450, GST, and p53, can also contribute to its development. Various unique forms of NMSC, like verrucous carcinoma and squamous cell carcinoma, result from viral infections [5,6]. Basal cell carcinoma (BCC), the most common skin cancer type, often stems from sunlight exposure. Despite a low death rate, it accounts for a substantial number of cases, reaching approximately 4.3 million annually in the US. Caucasians exhibit a notably higher prevalence. BCC manifests as flesh-colored bumps or areas on the skin and is primarily associated with areas exposed to sunlight. Genetic mutations and UV radiation are primary causes [7]. Squamous cell carcinoma (SCC), the second most common skin cancer, displays both benign and metastatic potential. It affects keratinocytes in the upper skin layer, appearing as rough red lumps [8]. UV-induced mutations, including P53 mutations, contribute to its development, with subsequent changes in various genes and signaling pathways. Melanoma, arising from melanocytes, presents a more peculiar yet significant challenge. UV light-triggered genetic changes can lead to uncontrolled melanocyte proliferation and cancer. Approximately 75% of skin cancer-related deaths are attributed to melanoma, emphasizing the importance of early detection. Its ABCD rule—assessing asymmetry, border irregularity, coloration, and diameter that helps diagnosing it. Melanoma subtypes, including superficial, nodular, lentigo maligna, and acral lentiginous, vary in appearance, location, and prognosis. While superficial melanoma is the most common subtype, nodular melanoma tends to grow vertically, delaying suspicion. Lentigo maligna commonly occurs in older individuals and can advance swiftly. Acral lentiginous melanoma is less common, often affecting areas unrelated to sun exposure [9,10]. Advanced cases may have worse prognoses, but ongoing research into immunotherapies and targeted drugs offers promise for improved treatment outcomes.

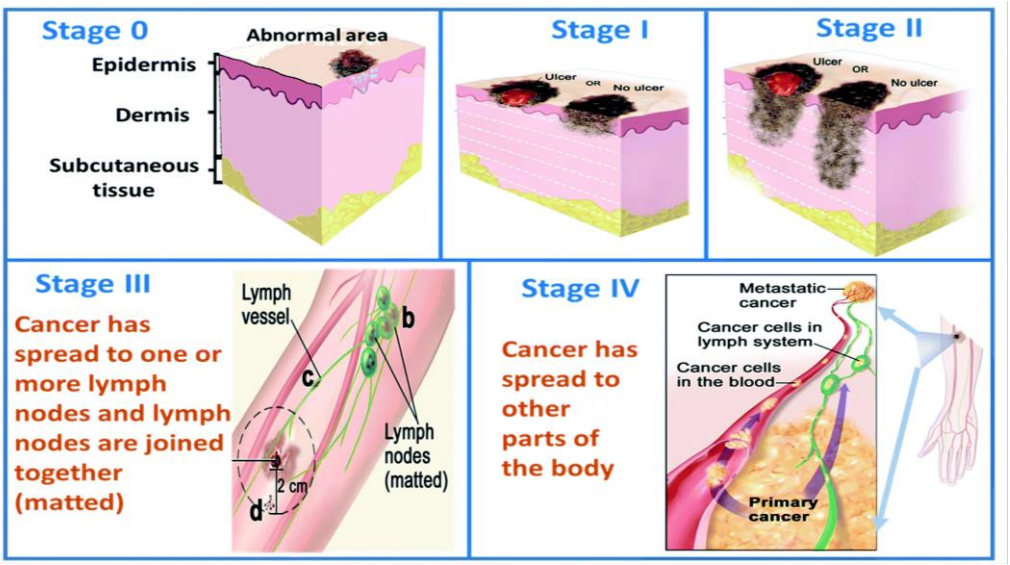

Figure 1. Different stages of skin cancer Reused from Narayanamurthy V et al. [10]

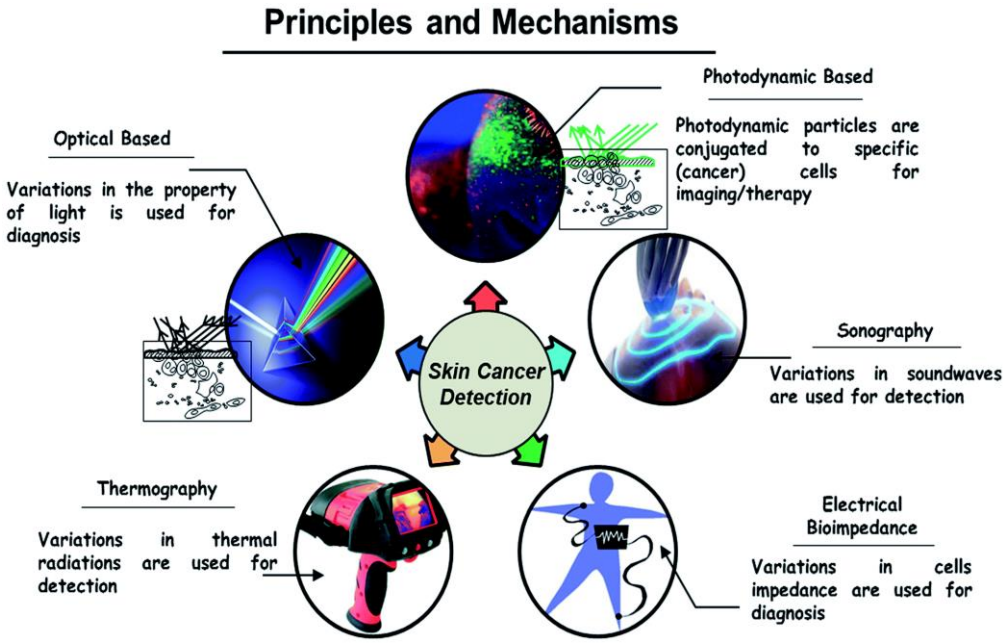

Figure 2. Different techniques for the diagnosis of skin cancer. Reused from Narayanamurthy V et al. [10]

2. HERBAL REMEDIES FOR SKIN CANCER

Skin cancer poses a significant challenge, underscoring the urgent need for innovative treatment approaches. Natural compounds derived from medicinal plants have demonstrated promising outcomes in inhibiting skin cancer cell growth and progression in various studies involving cell lines and animal models. The World Health Organization (WHO) has outlined dietary recommendations to mitigate cancer risks, emphasizing the importance of integrating phytochemicals from plants into daily consumption as both preventive and therapeutic agents. Epidemiological research has consistently highlighted the risk-lowering benefits of regular fruit and vegetable intake in the development of cancer. Phytochemicals sourced from medicinal plants, fruits, and vegetables have exhibited substantial roles in both preventing and treating skin cancer by modulating various molecular processes [11]. Detailed insights into these phytochemicals, their origins, and the specific molecular pathways are discussed in the following section. These compounds exhibit diverse functions, including inhibiting angiogenesis, metastasis, proliferation, inducing apoptosis, and halting cell cycle progression.

2.1 Ursolic acid (UA)

UA, found abundantly in herbs like thyme, basil, and rosemary, exhibits significant potential as a phytochemical. Its beneficial effects include anti-proliferative, chemo-preventive, antioxidant, and anti-inflammatory properties. In studies, UA triggered cell death in certain cancer cell lines through a cascade involving caspase-3 activation via mitochondria, while also influencing the expression of key proteins like p53 and caspase-3 and reducing Bcl-2 levels. Additionally, it affects cell cycle regulation, influencing the G1 phase and the expression of p21 WAF1, which governs cell cycle progression. UA has been shown to inhibit specific pathways like NF-κB signaling by affecting the phosphorylation of p65 and IκBα, leading to decreased expression of certain enzymes involved in cell proliferation. Notably, it demonstrated an ability to reduce UVB-induced oxidative stress in human lymphocytes by lowering lipid hydroperoxide levels and enhancing antioxidants when applied before UV exposure [12]. While there is ongoing interest in exploring UA's potential in combating skin cancer, no clinical trials on human skin have been reported thus far. However, a liposome-coating formulation containing UA, tested on three healthy subjects, showed an increase in ceramide content in human skin. Yet, the sample size in this experimental study was limited, and the examination was conducted solely on non-cancerous skin [13]. There remains an urgent necessity for extensive human studies on a larger scale specifically focusing on UA's effects on skin cancer.

2.2 Genisitic acid (GA)

GA, a potent isoflavone sourced from soyabeans, has been utilized in soy-rich diets as a supplement for conditions like cancer, heart diseases, and osteoporosis. This phytoestrogen present in soybeans demonstrates considerable potential in antioxidative, anti-inflammatory, anti-proliferative effects, and inhibition of certain

cancers, including breast, neuroblastoma, and both MM and NMSC cancers. It showcases multiple benefits such as anti-angiogenic effects, suppression of tumor growth and metastasis, cell cycle arrest, and facilitation of caspase-mediated cell death. GEN displays protective actions against UV-induced skin damage and photoaging-triggered skin cancer. It's been observed to inhibit the formation of pyrimidine dimers caused by UVB radiation and has demonstrated photoprotective properties by interfering with the cell cycle in models. Studies also reveal its ability to mitigate oxidative damage triggered by UVB exposure in the skin of mice [14]. In cancer cell cycle progression, GA targets various key elements like p53, p21, checkpoint kinase, and Chk2 in MM cells. Its impact extends beyond cell cycle regulation to include the inhibition of angiogenesis, as supported by numerous scientific findings. While there's substantial evidence supporting GEN's applications in preventing and treating MM and NMSC human skin cancers, further research encompassing in vitro and in vivo studies is crucial [15].

2.3 Luteolin

Luteolin, found in various foods like carrots, celery, olives, and peppers, exhibits significant potential as a phytochemical. It demonstrates promising anti-inflammatory, antioxidant, and anti-cancer properties, capable of inhibiting angiogenesis, promoting caspase-mediated cell death, and sensitizing cells to anticancer treatments across a wide spectrum of cancers [16]. Research indicates that luteolin encourages melanogenesis while diminishing the aggressive tendencies of skin cancer cells by influencing β3 integrin and focal adhesion kinase (FAK) signaling pathways. Moreover, luteolin induces apoptosis and halts the growth of skin cancer cells by adjusting the expression of key proteins like Bax and Bcl-2, along with attenuating ERK1/2 signaling [17]. While previous studies have highlighted the potential of this compound in cancer therapeutics, further investigations via in vitro and in vivo studies, as well as human clinical trials, are necessary to gain deeper insights into its efficacy and drug bioavailability.

2.4 Curcumin (CUR)

CUR, a potent compound derived from the rhizome of Curcumin longa, exhibits notable anti-inflammatory and antioxidant properties, particularly in conditions like psoriasis. Its impact extends to cancer prevention by modulating various pathways such as 5-lipoxygenase (5-LOX), COX-2, NF-κB, STAT3, phosphorylase kinase, and apoptotic cytokines [18]. As early as 1987, Kuttan et al. demonstrated CUR's anticancer potential in humans by reducing cancer lesion sizes in over 62 patients. Its efficacy extends to various cancers either as a standalone agent or in synergy with other therapeutic agents. Studies have explored CUR's protective effects against head and neck SCC, prostate, multiple myeloma, pancreatic, lung, and colorectal cancers. In a melanoma mouse model, CUR showcased its ability to upregulate miRNA-2015-5p expression, crucial in modulating apoptosis and proliferation. Furthermore, in a mouse skin model, CUR displayed anti-inflammatory effects against SRB12-p9 skin cancer cells by orally suppressing skin SCC growth and downregulating the pS6 biomarker. Additionally, CUR effectively inhibited proliferation in RB12-p9 cells at specific doses, suggesting its potential efficacy against skin cancer [19]. The safety and efficacy of CUR have been extensively studied in various clinical trials, positioning it as a robust compound for the development of medicines targeting skin cancer. Its administration through different routes, including oral and topical application, has demonstrated promising potential in mouse skin models.

2.5 Indole-3-carbinol (I3C)

Indole-3-carbinol (I3C) is a compound found abundantly in cruciferous vegetables like broccoli, Brussels sprouts, and cauliflower. Its cancer chemopreventive properties have been highlighted across various cancers such as breast, cervical, gastrointestinal, and lung cancers. Studies indicate that I3C induces cell cycle arrest and promotes apoptosis in UVB-sensitized MM cells by inhibiting Bcl-2 and reducing microphthalmia-associated transcription factor (MITF) expression [20]. Additionally, I3C hampers the proliferation of human MM cells by regulating phosphatase and tensin homolog (PTEN) degradation. In animal models, dietary supplementation with I3C has shown to enhance sensitivity to chemotherapy [21]. However, research on I3C has primarily been limited to cellular and mouse models. These initial findings call for extensive scientific investigation to validate its safety and efficacy before potential applications in clinical settings.

2.6 Resveratrol (RV)

Resveratrol (RV) is a stilbene polyphenol commonly found in mulberries, peanuts, and grapes. When topically applied, it exhibits robust inhibitory potential across the three different stages of carcinogenesis in murine models. It is known for its strong anti-cancer effects, RV possesses anti-proliferative, anti-inflammatory, and antioxidant properties. It acts as a potent scavenger for reactive oxygen species (ROS) and has demonstrated

the ability to reduce ROS levels in human skin fibroblast cells in vivo. Despite its antioxidant properties, RV counteracts anti-inflammatory actions by impeding the effects of COX-1 and COX-2, mainly through inhibition of NF-κB expression and suppression of p38 MAPK and ERK. RV shows promise in combination with other phyto-compounds by suppressing tumorigenesis and reducing epidermal hyperplasia while decreasing the expression of specific proteins and enzymes. It also exhibits potential as an adjuvant with other chemotherapeutic agents in treating MM with distant metastatic disease, decreasing skin cancer cell viability, and enhancing the cytotoxic effects of certain drugs. RV's effectiveness in sensitizing skin cancer cells to drugs like dacarbazine and influencing the expression of Akt/PKB proteins in MM cells showcases its potential as a chemotherapeutic agent [22,23]. However, RV administered orally shows poor bioavailability due to rapid clearance by the liver and intestines, limiting its concentration in the human body. Consequently, topical application of RV appears highly promising for both chemoprevention and chemotherapeutics. Clinical trials involving RV-containing creams have shown promising improvements in skin elasticity, hydration, and luminosity without adverse effects in non-cancerous individuals. Although these trials involved small sample sizes and focused on non-cancerous skin, initial results suggest potential efficacy [24]. However, comprehensive clinical trials exploring the efficacy and safety of RV in preventing and treating MM and NMSC are necessary.

2.7 Capsaicin

There is conflicting scientific evidence surrounding capsaicin's role as a carcinogenic agent or its potential for both chemoprevention and chemotherapy. While Hwang et al. showed in a mouse model that topical capsaicin use stimulated skin cancer by activating tyrosine kinase EGFR and COX-2, other studies found contrasting results. Some researchers observed no significant increase in skin cancer growth compared to controls and even noted a significant inhibition of papilloma formation in mice, suggesting capsaicin's potential in inhibiting skin cancer. Capsaicin has displayed strong chemopreventive and chemotherapeutic properties by influencing cell cycle arrest, apoptosis induction, and inhibition of cancer cell proliferation. It antagonizes the expression of NF-κB, AP-1, STAT3, and COX-2, contributing to its therapeutic effects. Additionally, capsaicin induces caspase-mediated cell death in human cutaneous SCC cell lines and exhibits anti-mitogenic activity on metastatic MM cells by down-regulating phosphatidylinositol 3-kinase (PI3-K) expression. Its synergistic effects in inducing caspase-mediated cell death in MM cell lines when combined with HA14-1 further demonstrate its potential [25,26]. Researchers are conducting further studies and epidemiological investigations to ascertain capsaicin's role in cancer therapeutics. However, while the topical application of capsaicin in treating skin cancer lacks comprehensive studies, experiences from capsaicin's use in other areas suggest potential drawbacks. One review noted that one in three patients experienced higher rates of side effects like stinging, erythema, and burning compared to a placebo when administered capsaicin topically. These adverse reactions could limit its application in skin cancer chemoprevention and chemotherapy [27]. Therefore, exploring novel drug delivery systems, designs, and formulations involving capsaicin with other agents that have fewer side effects might offer a new avenue for skin cancer treatment.

2.8 [6] - Gingerol

[6]-Gingerol, a potent phenolic compound extracted from the root of *Zingiber officinale*, was first studied by Park et al. in 1998. Topical administration showed potential in inhibiting skin papilloma formation. It also demonstrated anti-inflammatory properties by reducing epidermal ornithine decarboxylase activity, inhibiting COX-2, and suppressing NF-κB through modulation of p38 mitogen-activated protein kinase (MAPK) activity. Additionally, [6]-gingerol decreased intracellular ROS levels induced by UV radiation and activated caspases-3, 8, and 9, influencing antioxidant activity. Other strategies involve [6]-gingerol activating AP-1 DNA binding activity and modulating proteins like p53, Bax, Bcl-2, and surviving [28,29]. No human trials have been published so far, but ongoing investigations aim to incorporate [6]-gingerol into solid nanoparticles for topical administration to enhance safety, efficacy, and stability. Developing such a delivery system for [6]-gingerol could offer a more convenient and stable option for further human clinical studies.

2.9 Epigallocatechin-3-Gallate (EGCG)

EGCG, a potent phytocompound derived from *Camellia sinensis*, is extensively studied for its potential in both chemoprevention and chemotherapy, showcasing anti-inflammatory, anti-proliferative, and antioxidant properties within green tea phenols (GTP). Pioneering research by Katiyar et al. revealed GTP's ability to inhibit COX and lipoxygenase activity, reducing skin cancer load by diminishing epidermal hyperplasia and edema [30]. Topical application of EGCG showed a significant reduction in UV radiation-induced ROS products while inhibiting MAPK signaling cascades associated with these radiations. EGCG's anti-

proliferative functions involve modulation of NF-κB signaling cascades, inhibition of tumor-induced activator protein (AP-1), angiogenesis, and recruitment of T cells [31]. Moreover, studies by Nihal et al. highlighted EGCG's capacity to sensitize MM cells to interferon-induced growth inhibition, reduce cancer cell proliferation, and induce caspase-mediated cell death. The synergistic effect of EGCG with interferon displayed higher effectiveness than their individual applications. EGCG also downregulates inflammation, decreasing interleukin (IL)-1β secretion and NF-κB activity, resulting in reduced cancer cell growth. Recent research demonstrated EGCG's inhibition of MM cell invasion by reducing tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) function [32]. Human trials have showcased EGCG's strong therapeutic potential for skin cancer in various administration methods. While mice orally administered with GTP or through injection inhibited or reversed UV-induced skin papillomas, another study noted tumor inhibition in mice solely through topical application of EGCG. Topical GTP administration in humans provided protection against UV radiation-induced erythema. However, a single-blind randomized clinical trial on 50 individuals showed that orally administered GTP with vitamin C did not significantly reduce skin leukocyte infiltration and erythema compared to the placebo group [33]. These findings imply that topical use of EGCG holds higher potential than oral application for skin cancer chemoprevention and chemotherapy, warranting further research.

3. CONCLUSION

The exploration of herbal remedies for skin cancer presents a promising frontier in the quest for effective treatments. The utilization of bioactive compounds derived from medicinal plants unveils a potential avenue for inhibiting the development and progression of skin cancer cells. This avenue aligns with the World Health Organization's dietary recommendations, advocating for the integration of phytochemicals from natural sources into daily consumption for their chemopreventive and chemotherapeutic properties. Epidemiological studies consistently underscore the significance of regular fruit and vegetable intake in lowering the risk of cancer development, further emphasizing the potential of plant-derived compounds in this context. These phytochemicals, found in various natural sources, play pivotal roles in regulating molecular processes fundamental to skin cancer, offering a nuanced and multi-faceted approach to combating this disease. Their ability to influence angiogenesis, metastasis, proliferation, apoptosis, and cell cycle arrest positions these herbal remedies as potential candidates for targeted and comprehensive treatment strategies. As research continues to unravel the specifics of these compounds and their mechanisms of action, the integration of herbal remedies into skin cancer treatment protocols holds promise for more effective and holistic approaches to combating this pervasive disease.

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